PATHOLOGIC-DIAGNOSTIC
(Pulmonary Disease)

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Renewal
Application For Research Grant

Date: February 9, 1966

1. Name of Investigator: MAURICE S. SEGAL, M.D.

2. Title: Clinical Professor of Medicine

3. Institution & Address: The Boston City Hospital
Lung Station (Tufts)
818 Harrison Avenue
Boston, Massachusetts 02118

4. Project or Subject:

CHRONIC BRONCHITIS ENTITIES

5. Detailed Plan of Procedure (Use additional pages if more space is required.)

The Aim is to carry out an integrated study of ancillary and newly developed parameters to delineate the different types within the chronic bronchitis syndrome and their evaluation. The following procedures will be used:

1. The history and clinical condition of the patient

2. a) The physiological abnormality as measured by pulmonary function studies
and
b) blood (cellular and chemical) analyses

3. Sputum evaluation to include: physical, cytological, histochemical, chemical and bacteriological characteristics

4. Radiological evaluation by means of fluoroscopy, chest X-ray, bronchography and laminography

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5. Detailed Plan of Procedure:

A. Clinical Material

Patients to be studied in this project will be recruited from the Research Clinic at the Lung Station (Tufts), Boston City Hospital. Patients with "non-specific" chronic bronchitis, including the widest possible clinical spectrum, ranging from the young bronchitic through the terminal stages of bronchitis, emphysema and cor pulmonale, will be selected. We would estimate that a total of 200 to 300 patients will be studied over the full 3-year period.

"Non-specific" bronchitis for the purpose of this study will be defined as patients having chronic productive cough which has been present for at least 1 year, associated or not with non-paroxysmal wheezing and exhibiting signs of chronic air flow obstruction by either clinical, radiological and/or laboratory assessment.

Clinical, laboratory and X-ray evaluations will be performed at a time when the patients are free of acute exacerbations of bronchitis and/or evidence of clinical circulatory failure.

To attain this state, the patients will receive an intensive treatment designed to obtain maximal bronchial cleansing and bronchodilatation. This measure is designed to obtain at least 2 sets of clinical, physiological and sputum data and 1 adequate radiologic evaluation within the assumed "basal" condition period in order to standardize the method of data collection.

Repeated sets of studies will be done with at least 1-year intervals to follow the progression of disease. The patients will be evaluated clinically (and laboratory-wise) during this period to document their clinical course.

B. Methods of Evaluation

1. The Clinical Evaluation will include:

A detailed clinical history and physical examination, with particular emphasis on the character, duration and progression of symptoms. Etiological factors, such as smoking, history of acute diseases and respiratory offenders will be particularly stressed. This will include a clinical gradation of the level of bronchial inflammation which we have standardized at our Clinic.

2. Pulmonary Function Studies:

Each patient will have a basic profile of pulmonary function including spirometry, intrapulmonary mixing and respiratory gas

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exchange studies. Arterial blood studies will include: $Po_2$, $Pco_2$ and pH.

3. Sputum:

The patient will bring in a complete 24-hour sputum collection in a clean glass container. The examination will include: a) Gross description of its physical characteristics; b) Volume; c) Number of cells per ml. of sputum will be directly determined in a hemocytometer; d) Cover-slip smears of representative areas will be stained by Papanicolou's method for differential counts of the sputum cells. The following cell types will be differentiated: histiocytes (with emphasis on types of phagocytized materials), giant cells, bronchial epithelial cells (with emphasis on metaplasia and neoplasia), neutrophils (PMN's), eosinophils, lymphocytes, monocytes and plasma cells. The cytological data will be calculated to give the percentage of each cell type in the sputum. The total number of each cell type excreted per day will be calculated on the basis of this percentage, the sputum volume and the number of cells per ml.; e) A portion of a representative sample of the patient's sputum will be studied to determine the protein constituents of the sputum, using methods developed in this laboratory. Electrophoretic methods will be utilized, using fractions of the sputum separated by physical and chemical means. The sputum protein nitrogen content will be determined, using the Biuret method; f) An aliquot of the thickest portion of each specimen will be evaluated for adhesiveness and viscosity by methods developed in this laboratory; g) The remaining portion of the sputum will be cultured for bacterial pathogens, and comparable gram stains will be evaluated. Colony counts of the pathogens will be carried out, using the methods described by Laurenzi (Am. Rev. Resp. Dis., 86:106, 1962).

4. Radiological Studies:

a) Each patient will first have a set of conventional plain chest X-rays in full inspiration and expiration in the P-A position and at least in one lateral position.

b) Bronchography: Using a standard conventional procedure, the smallest possible amount of aqueous contrast media will be instilled to obtain a coating picture of the entire bronchial tree. P-A, oblique and lateral views will be obtained. The first stage of this procedure will entail a preliminary standardization of the technique in this group of patients with excessive cough and expectoration. Subsequently, bronchography will be performed in all the clinical ranges of chronic bronchitis with and without clinical evidence of established emphysema, secondary to chronic bronchitis.

c) Chest laminography will be added only in cases of chronic bronchitis with established emphysema for the complementary visualization of the vascular abnormalities (see 10, A-3).

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5. Pathology:

The facilities of the available general Pathology Department are not geared to complement the purposes of this project. We are, therefore, developing a section devoted to the specialized techniques required for lung pathology. The initial purpose of this section would be to set up methods for whole lung fixation and for the critical evaluation of bronchial biopsies as applicable to the patients in the study.

6. Methods of Analysis:

The method of collecting data has already been developed in cooperation with a statistical consultant. Processing and evaluation of data are still under consideration. It is expected that a final decision will be made during the the third year of the project when sufficient data is on hand for a valid projection.

Our goals will be directed toward:

a) Ascertaining the role of potential etiologic factors (e.g., infection, smoking, allergy, etc.)

b) The evolutionary pattern under well-controlled treatment

c) The determination of our ability to classify varieties of the chronic non-specific lung syndrome

d) Finally, evolving a suggested standardized terminology--classification of chronic obstructive lung disease

6. Budget Plan:

| | | |
|---|---|---|
| a) | Salaries | $ 42,188.00 |
| b) | Expendable Supplies | 3,500.00 |
| c) | Other Expenses | 1,000.00 |
| d) | Permanent Equipment | 1,500.00 |
| e) | Overhead (15% of a,b,c) | 7,003.20 |
| | Total | $ 55,191.20 |

7. Anticipated Duration of Work:

One more year within scope of present protocol; however, it would appear that 3-5 more years will be required.

8. Facilities and Staff Available:

A. Facilities:

The clinical, physiological and sputum studies will be entirely

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performed in the new expanded area of the Lung Station (Tufts). The Station is presently equipped with the basic major laboratory facilities necessary for this study. These include:

1. Equipment for pulmonary function studies: spirometers, multi-channel recorder, fast response gas analyzers for $CO_2$, $N_2$ and CO; electrodes for direct determination of blood $PO_2$, $Pco_2$ and pH.

2. Equipment for sputum studies: Complete setup for cytological and histochemical studies; binocular microscopes with microphotographic attachment and water bath. Bacteriological setup including inoculating room, autoclave, 2 incubators, media preparation facilities, etc.

3. Trained technicians

4. X-ray equipment: a new 300 Ma Keleket unit plus the facilities of the Central X-ray Department of the Boston City Hospital, including a special picker laminographic attachment and ceiling tube mount.

B. Staff

Maurice S. Segal, M.D.; Clinical Professor of Medicine (Principal Investigator)

Mauricio J. Dulfano, M.D.; Assistant Professor of Medicine (Physiology)

Sanford Chodosh, M.D.; Assistant Professor of Medicine (Bacteriology and Histochemistry)

Ernest J. Ferris, M.D.; Assistant in Radiology

James A. Shaka, M.D., Associate Professor of Pathology

Research Fellow; Ear, Nose and Throat Specialist (on fee basis)

Physiatrist (Pulmonary Physiotherapy) (on fee basis)

Technician; Bacteriology and Cytology

Technician; Pulmonary Physiology

Technician; Sputum Chemistry

Secretary

9. Additional Requirements:

-None-

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10. Additional Information (Including relation of work to other projects and other sources of support):

A. Previous Work Done on this Project and Related Fields

1. Clinical Studies:

During the past 10 years, our Station has accumulated a tremendous experience in the chronic bronchitis syndrome, and certain patterns are slowly emerging. These tentative patterns can be summarized as follows:

a) Progression of Symptoms

1. Chronic, episodic cough and expectoration, with interval-free periods.

2. Chronic, steady cough and expectoration

3. Chronic, progressive cough and expectoration

b) Sputum Characteristics

1. Mainly inflammatory mucosal involvement (indicated by predominance of cellular over glandular elements. The sputum is comparatively scanty).

2. Mainly mucid (bulky and "thicker")

3. Scanty, but tenacious expectoration (different physicochemical mucous character)

4. Combination of above

c) Syndrome Patterns

1. Starts as classic allergic bronchial asthma and progressively the bronchitis symptoms and signs supercede the asthmatic ones.

2. Starts with acute respiratory infection and over a short period of time, usually months, develops into severe ppogressive "asthmatic bronchitis".

3. Starts with shortness of breath predominantly and over the years develops progressive bronchitis signs with or without progressive shortness of breath.

4. Starts as specific endobronchitis (e.g., tuberculosis) and progresses into non-specific chronic bronchitis, even after the original reason has been controlled.

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5. Starts as a parenchymal disease and progresses into non-specific bronchitis (viral, sarcoid).

6. Chronic bronchtis, which mimics "pure emphysema". These are the patients with very discreet, but tenacious, expectoration. Still, this sputum has all the characteristics of inflammatory and/or infectious bronchitis. Because of it, there are few, if any, rhonchi or wheezing and, instead, silent areas and marked shortness of breath are present.

2. Sputum Studies:

A large experience has been accumulated in our laboratory. Evaluation of 4,000 sputum specimens in patients with "chronic bronchitis" has shown that the results are of statistical significance as indicators of early changes in the level of bronchial inflammation, and these determinations appear to be more sensitive than the clinical evaluation of the use of ancillary laboratory parameters like WBC and changes in the gross physical characteristics of sputum. Our special sputum studies acquired particular significance when analyzed in terms of follow-up changes for each individual. The clinical subgroups of bronchitis that were delineated were the "stable" patient without evidence of clinically acute bronchial inflammation (CB-S), the same type patient during the first few days of a clinically acute inflammatory episode (CB-AI). The differences that were noted between these groups were:

a) The blood polymorphonuclear neutrophils (PMN) alkaline phosphatase activity was significantly elevated in the BA-AI group vs. both other groups, although there was no discernable increase in WBC's or shifts-to-the-left. It is interesting that this response was generally lower than what has been observed in "normal" individuals with acute bacterial infection.

b) There is a significant increase in the mean number of PMN's excreted per day in the sputum between both the CB-S ($156 \times 10^6$) and CB-P ($320 \times 10^6$) groups and the CB-AI group ($847 \times 10^6$).

c) There is a similarly significant increase in the number of histiocytes excreted per day in the sputum, the values being respectively: CB-S ($3.5 \times 10^6$), CB-P ($3.8 \times 10^6$) and CB-AI ($12.5 \times 10^6$).

d) There is a significant increase in the number of bronchial epithelial cells excreted per day between the CB-S group ($18.1 \times 10^6$) and the CB-AI group ($64.9 \times 10^6$).

e) In the individual patient, these changes were often noted to begin before a clinically apparent acute inflammatory episode occurred. In addition, a further increase in histiocytes often occurred concurrently with the onset of clinical improvement.

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f) Significantly more of the sputum specimens demonstrated alkaline phosphatase activity in the histiocytes and bronchial epithelial cells in the CB-P group as compared to the CB-S group.

In a published study of 21 patients with chronic bronchitis, it was shown that during acute inflammatory processes, the excretion of all sputum cells was considerably increased, made up principally of neutrophil type, and certain differences in the type of epithelial cells excreted also occurred (Am. Rev. Resp. Dis., 85:635, 1962).

Methods for evaluating some of the physical characteristics of the sputum have been developed in our laboratory. A simple method for assessing the stickiness or "adhesiveness" and the thickness or "viscosity" has been tested in over 1,500 specimens. This involves the measurement of the time it takes the leading edge of an aliquot of sputum to reach successive distances in a 12 mm. tube on an inclined plane. When the time-distance relationships are plotted on semi-log paper, one can delineate a slope which seems to relate to "adhesiveness" and a second slope which seems to relate to "viscosity". Correlation of the mathematical expressions of these curves with pertinent symptoms of the patients at the time they raised the sputum show clear relationships of the measurement to symptoms referrible to sputum characteristics. We have been evaluating all of the study patients, utilizing these methods, but had not previously described the procedure.

The dry weight of the sputum samples is also being determined by drying aliquots of homogenized samples at 37°C. We are also recording the water loss rates on these specimens by periodic weighings during the drying process.

Over the past year, we have been working on methods to prepare sputum for protein separation by electrophoresis. By a sequence of ultrasonics and various precipitation methods, we have been able to prepare a clear fluid containing the dissolved sputum proteins. Electrophoresis of this material has resulted in rather clean separation of proteins. Although we still have to identify the proteins - for which purpose we plan to do concomitant serum protein electrophoresis and utilize immunologic techniques - it appears that we can begin to survey the study patient, using these techniques.

3. Laminographic Studies:

We have studied more than 80 patients by this technique. It has proven to be of extreme help in localizing even comparatively minor degrees of pulmonary vascular abnormalities in the presence of established chronic pulmonary emphysema. The pathological changes observed were: reduction in number of secondary branching; abnormal regional blood vessels crowding; signs of increased vascular resistance unequally distributed throughout the parenchyma and finally, massive disappearance of the peripheral circulation (Am. J. Roent., Rad. Ther. & Muc. Med., 88:1043, 1962).

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At the same time, we became aware of 2 facts: a) that in far advanced emphysema, the laminography could often detect gross abnormalities in the configuration of the bronchi supplying parenchymal areas where vascular derangement was detected and b) the need for adding a direct radiological approach, e.g., bronchography to clarify this relationship. Furthermore, it became obvious that laminography was a good tool only at the stages of advanced established emphysema, but not for the earlier changes or in the presence of pure chronic bronchitis. Bronchography performed in many of these patients has considerably increased the accuracy of detecting the relative participation of bronchial versus parenchymal involvement. Still, some patients with definite clinical and sputum manifestations of bronchitis may go undetected by bronchography. A major problem is the development of better techniques for this visualization, particularly the need for attaining maximal bronchial cleansing prior to bronchography and by using cinebronchographic sequences. Finally, and more important, a continuous attempt is being made by our group to learn from the findings in laminography and bronchography how to improve the plain chest X-ray reading (Radiologic Contributions to the Nosology of Obstructive Pulmonary Syndrome. Accepted for publication by Dis. Chest in 1965).

4. Community Chronic Lung Disease Study:

For the past year, we have been participating in a program designed to study methods for the postgraduate education of private physicians in the current trend in the diagnosis and treatment of chronic pulmonary disease. This has been carried out in cooperation with the Norfolk County TB and Health Association. Through this program, we have had the opportunity to apply many of the clinical and laboratory techniques described for the present study. This experience has been extremely valuable in the planning of this current research proposal.

5. Chronic Pulmonary Disease - Peptic Ulcer Interrelationships:

A mass of information was accumulated in the study of the relationship of chronic pulmonary disease to peptic ulcer disease and smoking habits. The data was previously submitted (June 12, 1963) to Dr. Hockett on 60 patients with chronic pulmonary disease (CPD) and 15 matched controls with chronic non-pulmonary disease (CD). The results indicated that although 52 per cent of the CPD group has reasonable evidence for peptic ulcer disease, 40 per cent of the CD group also had this finding. The non-smokers in the CPD group had a 44 per cent incidence. Also of interest is the finding that 18 per cent of the CPD group never smoked. It would appear that there are many etiologic factors to be considered in the understanding of chronic pulmonary disease. The occurrence of peptic ulcer disease seems to be related to factors of chronic illness in general, rather than specifically to chronic lung disease or smoking.

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B. Pertinent Literature References

In the past 5 years, there has been a flood of increasing interest in the field, but none of the proposed clinical classifications of the chronic bronchitis syndrome has found widespread acceptance. In view of this, the use of terminology such as "chronic non-specific obstructive pulmonary disease" (Ciba Guest Symposium, Thorax, 14:286, 1959) is wise at present.

A most recent attempt at a working classification has been put forward by Dr. P. Hugh-Jones (Boston City Hospital Lecture, April, 1963) who uses terms such as "non-paroxysmal asthma" (wheezing, asthmatic bronchitis); "simple bronchitis" (smoker's cough?); "infected bronchitis" (simple, plus infection?); "bronchitis and emphysema"; and "pure emphysema" (shortness of breath only). Within this working classification, he found that 2 clinico-pathological correlations seemed most important: "Pure infected bronchitis" usually exhibits centrilobular destruction, whereas "pure emphysema" usually is characterized by panacinar destruction.

This concept also has a physiological counterpart. In the bronchitis group, the obstructive element leads to some abnormalities in intrapulmonary gas exchange, whereas in emphysema the shortness of breath is mostly the result of abnormal mechanics of breathing.

Bronchography in recent years has shown its potentialities as a descriptive method in the study of chronic bronchitis.

Early bronchographic reports by Fisher, F.K. (In Roentgen Diagnosis by Scintz et al., English Editor, J.T. Case, London, 1953) describe generalized bronchial narrowing in bronchitis and in asthma, Simon (In Recent Trends in Chronic Bronchitis, N.C. Osward, Editor, Lloyd-Lude, London, 1958) describes different bronchographic patterns in chronic bronchitis such as peripheral pool, local dilatations of proximal bronchi, beading, peripheral lack of filling, etc. The description is quite extensive, but again, there is no clinical indentification of the entities responsible for these various changes, and they are all grouped within the chronic "bronchitis group".

Recently, a new important diagnostic step was added when Leopold and Seal (Thorax, 16:70, 1961) described the bronchographic appearance of centrilobular emphysema which was subsequently confirmed at autopsy. This pathological diagnosis was hitherto impossible to make in vivo.

Signature Maurice S. Segal M.D.
Director of Project

Richard H. Thorngren
Business Officer of the Institution
Accounting and Budget Officer

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